28. The method of claim 1, wherein said exendin analog or derivative has at least about 95% sequence similarity to the exendin of which it is an analog or derivative.

29. The method of claim 1, wherein said exendin analog or derivative is an analog or derivative of exendin-4.

30. The method of claim 1, wherein said subject is human.

REMARKS

The present invention relates to methods of regulating gastrointestinal motility. The invention is based in part on the surprising discovery that exendins are potent inhibitors of gastric emptying (see application, page 5, lines 15-16). As indicated in the specification, exendins are 39 amino acid peptides isolated from the oral secretions of the *Heloderma horridum* and *Heloderma suspectum* lizards. These peptides have not been found in any other reptile or mammal, and there is no known human counterpart to these lizard proteins. Despite this, Applicants made the further important discovery that exendins and exendin agonists, including exendin agonist analogs and derivatives are useful as inhibitors of gastric emptying for the treatment of, for example, diabetes mellitus and obesity in humans.

The present application claims novel methods for reducing gastric motility and slowing gastric emptying, comprising the administration of an exendin, for example, exendin-3, exendin-4, or other exendin agonist compounds which effectively bind to a receptor at which exendins exert their actions on gastric motility and gastric emptying.

Exendin agonist analogs and derivatives are identified as preferred, and the specification provides numerous examples of such compounds. As set forth above, Applicants have included the phrase "wherein the exendin agonist is an exendin analog or derivative" in claim 1. Exendin agonists are discussed in the specification, for example, at page 6, lines 4-10, and the application discusses exendin analogs and derivatives, for example, at page 17, lines 1-25 of the application. Claims 9, 20 and 21 have been amended to correct formalities and claims 12-19, drawn towards non-elected subject matter, have been cancelled without prejudice. New claims 22-30 are added. By this Response, Applicants have not added any new matter, and the Response is fully supported by the application as filed. In particular, support may be found, for example, at page 17, lines 1-25. This Response is not intended to, and may not, be construed as limiting the appropriate scope of protection provided under the doctrine of equivalents which should be applied to the fullest extent to protect Applicants from those who may misappropriate their invention by commercializing subject matter that is not substantially different from the claimed inventions. *See Hilton Davis Chem. Co. v. Warner-Jenkinson Co.*, 62 F.3d 1512, 1521-22, 35 USPQ2d 1641, 1648 (Fed. Cir. 1995) (en banc), *rev'd on other grounds*, *Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 41 USPQ2d 1865 (1997).

Applicants respond below in detail to each of the Examiner's questions in the non-final Office Action mailed July 9, 1999.

I. THE OBJECTION TO THE DRAWINGS

The Examiner has indicated that formal drawings will be required when the application is allowed. When the application is allowed, Applicants will submit formal drawings containing the amendments requested in Paper No. 7 (mailed with a certificate of mailing on September 8, 1998).

II. THE ELECTION/RESTRICTION

The Examiner has withdrawn the election of species requirement and agreed to examine all species of group 1 (i.e., claims 1-11 and 20-21). The restriction requirement was made final and claims 12-19 drawn to non-elected inventions were withdrawn from consideration. In an effort to expedite issuance, Applicants have canceled non-elected claims 12-19 without prejudice. The cancellation of these claims is not intended to constitute, does not constitute, and may not be construed to constitute an admission against interest regarding the patentability of this subject matter.

III. THE SEQUENCE RULE OBJECTION

The Examiner requests that Applicants submit a new sequence listing in a computer readable form which includes the sequences that were cited in claims 20 and 21. In order to advance prosecution, Applicants have enclosed a new sequence listing as requested by the Examiner. In view of the above, Applicants respectfully request that the Examiner reconsider and withdraw this objection. Applicants' submission of a new sequence listing as requested by the Examiner is not intended to constitute, does not constitute, and may not

be construed to constitute an admission against interest regarding Applicants' compliance with the patent law or any PTO Rules.

IV. THE OBJECTION TO CLAIMS 20 AND 21

Claims 20 and 21 stand objected to as allegedly not complying to 37 C.F.R. §1.821 (d). In order to advance prosecution and expedite issuance, Applicants have amended claims 20 and 21 to make reference to the appropriate sequence identification numbers as requested by the Examiner. In view of the above, Applicants respectfully request that the Examiner reconsider and withdraw this objection. Applicants' amendment of claims 20 and 21 to include sequence identification numbers as requested by the Examiner is not intended to constitute, and does not constitute any admission against interest regarding Applicants' compliance with the patent law or any PTO Rules and may not be so construed.

V. THE SECTION 112, SECOND PARAGRAPH, REJECTION

Claims 1-11, 20, and 22 stand rejected under 35 U.S.C. 112, second paragraph, as allegedly being indefinite.

Under 35 U.S.C. § 112, paragraph 2, a specification shall include one or more claim "particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention." According to the case law, this means only that a claim must reasonably apprise those skilled in the art of the scope of the patent, *see Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385, 231 USPQ 81, 94-95 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987). Determining whether a claim is

indefinite requires an analysis of "whether one skilled in the art would understand the bounds of the claim when read in light of the specification. . . . If the claims read in light of the specification reasonably apprise those skilled in the art of the scope of the invention, [section] 112 demands no more." *Miles Lab., Inc. v. Shandon Inc.*, 997 F.2d 870, 875, 27 USPQ2d 1123, 1126 (Fed. Cir. 1993), *cert. denied*, 114 S. Ct. 943 (1994). *See also Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 927 F.2d 1200, 1217, 18 USPQ2d 1016, 1030 (Fed. Cir. 1991); *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 806 F.2d 1565, 1576, 1 USPQ2d 1081, 1088 (Fed. Cir. 1986) (citations omitted); *Seattle Box Co. v. Industrial Crating & Packing Inc.*, 731 F.2d 818, 826, 221 USPQ 568, 574 (Fed. Cir. 1984); *In re Morasi*, 710 F.2d 799, 803, 218 USPQ 289, 292 (Fed. Cir. 1983). The law of definiteness is simply a requirement that claims must "reasonably apprise those skilled in the art" as to their scope and be "as precise as the subject matter permits." *Shatterproof Glass Corp. v. Libbey-Owens Ford Co.*, 758 F.2d 613, 624, 225 USPQ 634, 641 (Fed. Cir. 1985).

The Examiner alleged that claim 1 recites "an incomplete method." She further alleged that it is "not clear how administration of an exendin or exendin agonist will result in 'beneficial regulation of gastrointestinal motility'." Applicants maintain that the claim is definite as written, *i.e.*, that those skilled in the art would understand what is claimed when the claim is read in light of the specification. One of ordinary skill in the art reading the claim would certainly understand the nature of the language "beneficially regulating" in light

of the specification. Such comprehension is all that is required by second paragraph of section 112.

To the extent that the Examiner is further suggesting that Applicants must know how their invention works, Applicants submit that there is no legal basis for this. The PTO may not require that a claim to a method of beneficially regulating gastric emptying with a compound include a declaration of "how administration of the exendin or exendin agonist will result in 'beneficial regulation of gastrointestinal motility'."[1]

Thus, while Applicants have amended claim 1 to specifically recite that the method involves "beneficially regulating said gastrointestinal motility in said subject," there is no legal requirement that such language be included. Applicants have amended claim 1 solely in order to speed the prosecution of this matter and only because the amendment does not alter the scope of the claim. Accordingly, Applicants' amendment of claim 1 to include the recitation previously found in the preamble is not intended to constitute, and does not constitute any admission against interest regarding Applicants' compliance with the patent law or PTO Rules and may not be so construed.

The Examiner also questioned the recitation of "therapeutically effective amount" in claim 1 on the assertion that there is no definition of what constitutes a therapeutically

1. In fact, the law provides the opposite. *See Newman v. Quigg*, 877 F.2d 1575, 1581, 11 USPQ2d 1340, 1345 (Fed. Cir. 1989) (observing that "it is not a requirement of patentability that an inventor correctly set forth, or even know, how or why the invention works"); *Fromson v. Advance Offset Plate, Inc.*, 720 F.2d 1565, 1570, 219 USPQ 1137, 1140 (Fed. Cir. 1983) ("[I]t is axiomatic that an inventor need not comprehend the scientific principles on which the practical effectiveness of his invention rests.").

effective amount in the specification. Applicant respectfully submits that this term is clear and definite and directs the Examiner's attention to the decision and opinion in *Key Pharmaceuticals v. Hercon Laboratories Corp.*, 161 F.3d 709, 48 USPQ2d 1911 (Fed. Cir. 1998). *Key Pharmaceuticals* involved a claim to a "drug-in-adhesive" transdermal patch that included a requirement for a "pharmaceutically effective amount" of a drug. The claim read:

> 12. An adhesive transdermal layer for sustained release of a pharmaceutically active drug to the skin of a human patient, comprising:
>
> a pharmaceutically active drug-containing essentially planar sheet of an at least partially cross-linked acrylic adhesive, said essentially planar sheet comprising a flexible self-supporting cross-linked acrylate polymer of sufficient adhesivity, durability and strength whereby intimate diffusional contact with skin of the patient is maintained for a period of at least about 24 hours without destruction of the physical integrity thereof, said essentially planar sheet being capable of retaining dispersed therein *sufficient pharmaceutically active drug to deliver to the skin a pharmaceutically effective amount of said pharmaceutically active drug over a 24-hour time interval*, without dissolution of the at least partially cross-linked acrylic pressure-sensitive adhesive [emphasis by the Court].

According to the Federal Circuit, the involved patent did not provide any numerical values for what is meant by "a pharmaceutically effective amount." The court went on to hold, however, that the claim was properly interpreted to mean the minimum daily dosage of the drug approved by the FDA as of the filing date of the application for the patent (at least 2.5 mg/day). The Federal Circuit, speaking through Judge Plager, held that the district court's determination that the phrase "pharmaceutically effective amount" in the transdermal patch claim meant the FDA-approved minimum dosage was "logical and appropriate" (citing

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Additionally, it is that law that a claim need not recite how an invention works.

Markman, 52 F.3d at 986 ("[I]n construing disputed terms in claim language ... [,] the focus is on ... what one of ordinary skill in the art at the time of the invention would have understood the term to mean."). *See also In re Watson*, 517 F.2d 465, 476-477, 186 USPQ 11 (CCPA 1975)("an effective amount of a germicide suitable for use in oral hygiene" is not indefinite; "The very term 'germicide,' used in this claim, indicates that germicidal action is the effect sought to be produced");[2] *In re Spiller*, 500 F.2d 1170, 1180-1181, 182 USPQ 614 (CCPA 1974)(in claim for paper manufacture, phrase requiring use of starch "in amount sufficient to be capable of causing selective modification of surface properties'' is not indefinite; "the claims make it clear, through the use of the work 'selective', that any modification of surface properties is subjectively desirable in the particular coating applied."). *Ex parte Skuballa*, 12 USPQ2d 1570, 1571 (Bd. Pat. App. & Int'f 1989) (claim to an "effective amount" of a certain compound is not indefinite even though the specification recites "diverse utilities": "We are satisfied that the skilled worker in this art

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2 *In re Frederiksen*, 213 F.2d 547, 102 USPQ 35 (CCPA 1954), is not to the contrary. In that case, the court held that "the statement 'effective amount' is on its face indefinite since it fails to state the function which is to be rendered effective." Thus, *Frederiksen* is authority for the proposition that the phrase "an effective amount" is indefinite when the claim fails to state the function that is to be achieved. The appealed claim in Frederiksen recited "an effective amount of the diethylamino ethanol ester of phenaceturic acid." The claim completely failed to state the effect sought to be produced.

The present case is distinguishable, however, since claim 1 recites an "effective amount of an exendin or an exendin agonist" for "beneficially regulating . . . gastrointestinal motility." Moreover, the claim language must be read in light of the application disclosure as it would be interpreted by one of ordinary skill in the art. *See In re Moore*, 58 CCPA 1042, 439 F.2d 1232, 169 USPQ 236 (1971). Those skilled in the art will be able to determine from the disclosure, including the examples, what an effective amount of an exendin agonist is. In the context of the claimed subject matter, the disputed phrase reasonably defines the metes and bounds of the invention to one of ordinary skill in the art. *See In re Halleck*, 57 CCPA 954, 422 F.2d 911, 164 USPQ 647 (1970); and *In re Fuetterer*, 50 CCPA 1453, 319

could readily optimize effective dosages and administration regimens for each of the recited utilities.").). *Compare Rhone-Poulenc Agrochime S.A. v. Biagro Western Sales, Inc.*, 35 USPQ2d 1203, 1205 (E.D. Calif. 1995) (method for "controlling" fungus with "effective amount" of compound is not indefinite; "a term is only indefinite if one skilled in the relevant art would not understand what is claimed even when the claim is read in light of the specification."). See, furthermore, page 28, line 2-page 29 line 11 of the instant application where various proposed dosages are described in detail.

With respect to claim 9, the Examiner suggests changing "said gastric motility" to "said gastrointestinal motility." Applicants have amended claim 9 as suggested by the Examiner and thus this issue is now moot.

In view of the above, Applicants respectfully request that the Examiner reconsider and withdraw this rejection.

VI. THE SECTION 112, FIRST PARAGRAPH, REJECTION

Claims 20 and 21 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly not being enabled. The Examiner states that the specification teaches the use of exendin-4 analogs, but alleges that the specifications provide inadequate guidance for the use of most of the possible exendin analogs encompassed by claims 20 and 21. In particular the Examiner further alleges that the specification provides no guidance to one

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F.2d 259, 138 USPQ 217 (1963). The claims are not indefinite under § 112, second paragraph.

of skill in the art regarding which substitutions of amino acids in exendin-3 or exendin-4 would result in compounds useful in a method for regulating gastro-intestinal motility.

Applicants respectfully traverse the rejection. In order to enable a claimed invention, all that is required is to provide sufficient information that one skilled in the art can make and use the claimed invention. Thus, the PTO has itself recognized that limiting an applicant to the preferred materials in the absence of limiting prior art does not serve the constitutional purpose of promoting the progress in the useful arts. M.P.E.P. §2164.08(c).

It is well settled, furthermore, that patent applicants are not required to disclose and test every species that may be encompassed by their claims, even in an unpredictable art. *In re Angstadt*, 537 F.2d 498, 502-03, 190 USPQ 214, 218 (CCPA 1976). Indeed, it is not even required that every embodiment in a disclosure be operative in order to be enabling under 35 USC 112, first paragraph. *Atlas Powder Co. v. E.I. Dupont de Nemours & Co.*, 750 F.2d 1569, 224 USPQ 409 (Fed. Cir. 1984); *In re Geerdes*, 491 F.2d 1260, 180 USPQ 789 (CCPA 1974).

Indeed, the concerns raised in the Office Action are of the type that were long ago rejected by the Court in *In re Fuetterer*, 138 USPQ 217 (CCPA 1963) (Rich, J.). There, speaking through Judge Giles S. Rich, co-author of the 1952 Patent Act and 43-year member of the CCPA and the Court of Appeals for the Federal Circuit, the court considered an appeal from a rejection of claims to a rubber stock for producing tire treads.

The claimed rubber stock included "an inorganic salt" that was defined only by being "capable of holding a mixture of [a previously referred to] carbohydrate and [a previously referred to] protein in colloidal suspension in water." *Id.* at 219. The Board had affirmed the rejection of the claim as "unduly broad." Judge Rich promptly disposed of this rejection as unsound and stressed that patent applicants must be able to obtain claims that adequately protect their inventions, even though some experimentation may be required to determine if a product or method falls within the scope of the claim. Judge Rich described Fuetterer's claim and the PTO rejection as follows:

> The rejection of the claims for "undue breadth" places particular emphasis on (1) an alleged "undue burden upon the public to determine what salts are suitable for obtaining the desired results" (emphasis ours), and (2) an alleged "undue [amount of] experimentation" required of those skilled in the art to determine those salts possessing the "function asserted" by the instant claims. The undue breadth rejection phase of the instant case appears in the following posture. Appellant has described his invention as comprehending the use therein of any inorganic salt capable of performing a specific function in a specific combination and he has disclosed specifically four such salts which are capable of performing this function. The examiner and the board, believing that not all inorganic salts are capable of performing this function and that one skilled in the art would not know offhand which inorganic salts are capable of so functioning, have rejected the claims as "unduly broad."

Id. at 222-223. According to Judge Rich, however, this was all "beside the point" and could not support the PTO's rejection:

> We find the arguments of the board and the examiner relating to experimentation necessary to determine the suitability of undisclosed salts to operate in appellant's claimed combination beside the point. Appellant's invention is the combination claimed and <u>not the discovery that certain inorganic salts have colloid suspending properties. We see nothing in</u>

> patent law which requires appellant to discover which of all those salts have such properties and which will function properly in his combination. The invention description clearly indicates that any inorganic salt which has such properties is usable in his combination.

Id. at 223 (emphasis added).

In *In re Fuetterer*, Judge Rich further emphasized that an applicant's claims may not be restricted so that they are easily avoided simply by identifying an undisclosed compound that will work:

> If others in the future discover what inorganic salts additional to those enumerated do have such properties, it is clear appellant will have no control over them per se, and equally clear his claims should not be so restricted that they can be avoided merely by using some inorganic salt not named by appellant in his disclosure. The only "undue burden" which is apparent to us in the instant case is that which the Patent Office has attempted to place on the appellant.

Id. (emphasis added). Similarly, if others in the future discover other exendin analogs or derivatives aside from those set out in applicant's specification with the ability to regulate gastrointestinal motility, applicant will have no control over them *per se*. Nevertheless, following *In re Fuetterer*, it is plain that under the law applicant's claims cannot be restricted by the PTO so that they can be avoided merely by using some compound not named in his disclosure.

The claims, as amended, recite methods of regulating gastrointestinal motility by administering an exendin or exendin analog or derivative. Here, there is no evidence that those skilled in the art could not readily make or test known or later-developed exendin

analogs or derivatives for their ability to regulate gastrointestinal motility. Indeed, the application describes methods for evaluating the effects of exendins and exendin agonists on gastric motility in Examples 1-3 and notes that other art-known or equivalent methods may also be used (see application, page 13, lines 8-13). One such method for identifying or evaluating the ability of a compound to slow gastric motility is provided in the paragraph spanning pages 13 and 14 of the application. In view of the cases cited above, it would be improper to limit Applicant to use of preferred materials when such claims might be attempted to be avoided merely by using different exendin agonist analogs or derivatives that could be readily made and tested given the information in the present application. Applicants respectfully request that the Examiner reconsider and withdraw this rejection.

VII. THE SECTION 102 REJECTION

Claims 1-3 stand rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Dupre *et al.* as evidenced by either Goke *et al.* or Rai *et al.* The Examiner states that Dupre *et al.* teaches that truncated glucagon-like peptide 1 has been shown to retard gastric emptying of food in normal humans. The Examiner argues that GLP-1 is an exendin receptor agonist because truncated GLP-1 allegedly binds to the same receptor as do exendin-4 and exendin-3. Thus, the Examiner concludes that Dupre *et al.* teaches a method of delaying gastric emptying (and therefore regulating gastric motility and gastro-

intestinal motility), that is the same as that claimed. Applicants respectfully traverse the rejection.

In order to reject a claim as being anticipated, the burden is on the PTO to show that each and every element set forth in the claim is described in a single prior art reference. Here, amended claim 1 recites that the method of regulating gastrointestinal motility involves administering an exendin or an exendin agonist, wherein the exendin agonist is an exendin analog or derivative. The Dupre *et al.* article cited by the Examiner relates to the role of human glucagon-like peptide ("GLP-I") in retarding gastric emptying. Applicant respectfully submits that those skilled in the art will understand GLP-I is not an exendin agonist, much less an exendin analog or derivative. An exendin agonist is defined as a compound that mimics the effects of exendins on gastric motility and gastric emptying, namely, a compound which effectively binds to the receptor at which exendins exert their action on gastric motility and gastric emptying (see application, page 6, lines 4-10). However, the application shows that the exendins were about 170-290 times more potent than GLP-1[7-36]NH_2 in inhibiting gastric emptying (see application, page 23, lines 10-13). The application also shows that the effects of exendins and exendin agonists are not due to binding at the cloned GLP-1 receptor, but a separate receptor (see application, page 24, lines 5-23 and page 33, lines 15-19).

Furthermore, exendin analogs or derivatives are functional variants having similar amino acid sequence and retaining, to some extent, at least the gastric motility- and

gastric emptying- related activities of the related exendin (see application, page 17, lines 2-6). However, the amino acid sequence of GLP-1 is only about 53% similar to that of exendins and, as noted above, GLP-1 is about 170-290 fold less potent than exendin-3 and exendin-4, which act at a receptor distinct from the GLP-1 receptor. Thus, the Dupre *et al.* article fails to describe a method of regulating gastrointestinal motility with an exendin or an exendin agonist, wherein the exendin agonist is and exendin analog or derivative and thus fails to anticipate the claimed invention.

Applicants note that nothing in the Goke *et al.* or Rai *et al.* articles indicates that GLP-1 is an exendin agonist, much less an exendin analog or derivative, as those terms are used in the present application. The Goke *et al.* article merely concludes that exendin-4 is an agonist and exendin (9-39) amide is a specific GLP-1 receptor antagonist. However, as noted above, the facts indicate that the converse is not true, *i.e.*, GLP-1 is not an exendin agonist.

The Rai *et al.* article states that truncated glucagon like peptide 1 is a mammalian analogue of exendin-3 and exendin-4, but uses the term "analogue" to mean something different from Applicants. In particular, Applicants state:

> Exendin analogs or derivatives are functional variants having similar amino acid sequence and retaining, to some extent, at least the gastric motility - and gastric emptying-related activities of the related exendin. By "functional variant" is meant an analog or derivative which has an activity that can be substituted for one or more activities of a particular exendin.

The Rai *et al.* article clearly does not indicate that truncated GLP-1 is an exendin agonist analog as defined above. For example, Figure 1 of Rai *et al.* shows significant differences between the amino acid sequence of truncated GLP-1 and either of exendin-3 or exendin-4. Nor is there anything in Rai *et al.* that contradicts Applicants results showing exendins to be about 170-290 fold more potent than GLP-1. Thus, Applicants respectfully submit that GLP-1 is not an exendin, an exendin agonist, or an exendin analog or derivative and that the Dupre *et al.* article dealing with GLP-1 therefore fails to anticipate the claimed invention.

In view of the above, Applicants respectfully request that the Examiner reconsider and withdraw this rejection.

VIII. THE SECTION 103 REJECTION OF CLAIMS 4 AND 5

Claims 4 and 5 stand rejection under 35 U.S.C. §103 (a) as allegedly being unpatentable over Dupre *et al.* in view of Rai *et al.* The Examiner argues that it would have been obvious to one of skill in the art at the time the invention was made to have substituted either exendin-3 or exendin-4 for GLP-1 in the method of delaying gastric emptying taught by Dupre *et al.* One allegedly would have been motivated to make the substitution because the use of a more potent compound would have reduced the required dose and thus would be expected to have fewer side effects. According to the Examiner, one would have had a reasonable expectation of success because exendin-3, exendin-4, and GLP-1 are agonists of the same receptor.

Applicants respectfully traverse. In addition to the arguments set forth above with respect to these documents, Applicants not that in order to establish a *prima facie* case obviousness, the burden is on the PTO to show some suggestion or motivation in the prior art to modify or combine alleged references in a manner that yields all of the claim limitations with a reasonable expectation of success. Here, the claimed invention relates to regulating gastrointestinal motility by administering an exendin or an exendin agonist, wherein the exendin agonist is an exendin analog or derivative. The Dupre *et al.* article recites a presumption that pharmacological doses of GLP-1 led to a reduction in "glycemic excursions after meals" by a mechanism that may have involved "delayed gastric emptying." The Rai *et al.* article states that an increase in cellular cAMP and pepsinogen secretion is observed with concentrations of the exendins that are 10-fold lower than those required with "TGLP-1." There is no evidence or reason to explain why one of ordinary skill in the art, at the time of the present invention, allegedly would have been motivated to use exendin-3 or exendin-4 to regulate gastrointestinal motility *in vivo*, merely based on the in vitro results of Rai *et al.*, nor that one of ordinary skill in the art would have had a reasonable expectation of success based on such limited information.

Applicants note that it is improper to reconstruct the claimed invention in hindsight using the specification as a template or blueprint. Applicants respectfully submit that a prima facie case of obviousness has not been established. In any event, Applicants'

results showing that exendins are about 170-290 fold more potent than GLP-1 would constitute surprising and unexpected results and thereby rebut any such *prima facie* case.

In view of the above, Applicants respectfully request that the Examiner reconsider and withdraw this rejection.

IX. THE SECTION 103 OF CLAIMS 6-8

Claims 6-8 stand rejected under 35 U.S.C. §103 (a) as allegedly being unpatentable over Dupre *et al.* in view of either Chernish *et al.* or Kolterman *et al.* and in further in view of Eng. The Examiner suggests that it would have been obvious to one of skill in the art to combine the teaching of Chernish *et al.* or of Kolterman *et al.* with that of Dupre *et al.* to make the claimed invention. According to the Examiner, one would have been motivated to substitute an exendin agonist such as GLP-1 for a glucagon because GLP-1 may disrupt fuel metabolism less than does glucagon.

Applicants respectfully traverse. As noted above, the claimed invention relates to the use of exendin or an exendin agonist, wherein the exendin agonist is an exendin analog or derivative, to regulate gastrointestinal motility. Thus, even if the Examiner's assertions that one would have been motivated to use GLP-1 to regulate gastrointestinal motility were correct, which Applicants dispute, this would fail to suggest the claimed method. GLP-1 is not an agonist of exendin, and is not an exendin analog or derivative.

In view of the above, Applicants respectfully request that the Examiner reconsider and withdraw the above rejection.

X. THE SECTION 103 REJECTION OF CLAIMS 9-11

Claims 9-11 stand rejected under 35 U.S.C. §103 (a) as allegedly unpatentable over Dupre *et al.* in view of Daniel *et al.* and further in view of Eng. The Examiner states that given that Eng teaches that exendin and GLP-1 may be metabolically safe and that Daniel teaches that a side-effect of glucagon administration is occasional nausea and vomiting, it allegedly would have been obvious to one skilled in the art at the time the invention was made to combine the teachings of Dupre *et al.* with that of Daniel *et al.* and Eng to make the claimed invention. The Examiner states that one would have been motivated to substitute GLP-1 for glucagon in the method of Daniel for the reasons given above in the discussion of claims 6-8.

Applicants respectfully traverse. As noted above, GLP-1 is not an exendin agonist, nor is it an exendin analog or derivative. Thus, even if one skilled in the art would have been motivated to substitute GLP-1 for glucagon in the method of Daniel, which Applicants contest, this would still fail to render the claimed invention obvious.

In view of the above, Applicant respectfully requests that the Examiner reconsider and withdraw this rejection.

CONCLUSION

Applicants believe that all claims are in condition for allowance and respectfully request early Notice thereof. Should any issues or questions remain, the Examiner is encouraged to telephone the undersigned so that they may be promptly resolved.

The Commissioner is hereby authorized to charge any additional fees that may be incurred or credit any overpayment of fees to our Deposit Account No. 12-2475.

Respectfully submitted,

Dated: January 10, 2000 By: _____

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